REMARKS

Status of the Claims

Claims 2, 3, 6, 9-19, 21-35, 37-47 and 49-84 are pending in the application.

Claims 21-27 and 49-83 have been withdrawn from consideration by the Office on the basis that they are drawn to non-elected subject matter.

Claims 2, 3, 6, 10-11, 16, 28-34, 38-39 and 84 have been amended with entry of this amendment.

Claim 35 has been cancelled without prejudice or disclaimer with entry of this amendment.

Claims 2, 3, 6, 9-19, 28-34, 37-47 and 84 remain under consideration with entry of this amendment.

Summary

Claims 2, 3, 6, 9-19, 28-35, 37-47 and 84 are pending in the application and were examined in the Office Action dated 24 December 2008. In the subject Action, the following claim rejections have been raised: **(a)** claim 6 stands rejected under 35 U.S.C. §112, second paragraph, as indefinite; **(b)** claims 6 and 34 stand rejected under 35 U.S.C. §112, second paragraph, as indefinite; and **(c)** claims 2, 3, 6, 9-19, 28-35, 37-47 and 84 stand rejected under 35 U.S.C. §103(a) as unpatentable over U.S. Patent No. 6,331,311 to Brodbeck et al. ("Brodbeck '311") in view of U.S. Patent No. 6,130,200 to Brodbeck et al. ("Brodbeck '200") and Penco et al (1998) *Polymer International* 46:203-216 ("Penco") and Ravivarapu et al. (2000) *European Journal of Pharmaceutics and Biopharmaceuticals* 50:263-270 ("Ravivarapu"). Applicants respectfully traverse all pending claim rejections for the following reasons.

Overview of the Amendment

Applicants, by way of this amendment, have cancelled certain claims and amended certain other claims to remove obvious typographical errors and/or to recite the invention with greater particularity. More specifically, claim 35 has been cancelled

without prejudice and disclaimer. Cancellation of this claim is not in acquiescence to any objection or grounds of rejection raised by the Office, and applicants expressly reserve their right to bring the claim again in another related application. Claims 2, 3, 6, 10-11, 16, 28-34, 38-39 and 84 have been amended to remove unnecessary language, to correct obvious typographical and grammatical errors, and to recite the claimed invention with greater specificity. Support for these amendments can be found in the claims as originally filed and throughout the specification. Accordingly, no new matter has been added by way of the amendments to the claims, and the entry thereof is respectfully requested.

The Rejections under 35 U.S.C. §112, Second Paragraph

Claim 6 stands rejected under 35 U.S.C. §112, second paragraph, on the basis of improper antecedent basis for the limitation "medium molecular weight (MMW) polymer". Office Action at page 2. In response, applicants draw the Office's attention to the amendment to claim 6, whereby applicants have removed the language objected to by the Office. Reconsideration and withdrawal of the rejection of claim 6 under U.S.C. §112, second paragraph, is thus earnestly solicited.

Claims 6 and 34 stand rejected under 35 U.S.C. §112, second paragraph, on the basis of indefiniteness. In particular, the Office has objected to the recited ranges for the various polymers, in particular, the inclusion of 0% in those ranges. Office Action at page 3. In response, applicants draw the Office's attention to the amendments to claims 6 and 34, whereby applicants have removed the language objected to by the Office. Reconsideration and withdrawal of the rejection of claims 6 and 34 under U.S.C. §112, second paragraph, is thus earnestly solicited.

The Rejection under 35 U.S.C. §103

Claims 2, 3, 6, 9-19, 28-35, 37-47 and 84 stand rejected under 35 U.S.C. §103(a) as unpatentable over Brodbeck '311 in view of Brodbeck '200, Penco and Ravivarapu. Simon as applied in the Section 102 rejection above and in further view of Cleary. Applicants respectfully traverse the rejection for the following reasons.

In pertinent part, 35 U.S.C. §103 provides that a patent may not be obtained "if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious to a person having ordinary skill in the art." 35 U.S.C. §103. Any analysis under Section 103 must consider the following factual inquiries: (1) the scope and content of the prior art; (2) the level of ordinary skill in the art; (3) the differences between the claimed subject matter and the prior art; and (4) secondary considerations of non-obviousness (such as commercial success and long-felt but unsolved need, failure of others, and unexpected results). *Graham v. John Deere Co.*, 383 U.S. 1, 17-18, (1966) (the "*Graham* factors"). The Supreme Court, in *KSR Intern. Co. v. Teleflex, Inc.*, 550 U.S. 398 (2007) reaffirmed that the *Graham* factors "continue to define the inquiry that controls" an obviousness analysis. Accordingly, to establish a *prima facie* showing of obviousness the Office must adhere to the following analysis: (a) the claimed invention must be considered as a whole; (b) the references must be considered as a whole; (c) the references must be viewed without the benefit of impermissible hindsight vision afforded by the claimed invention; and (c) reasonable expectation of success is the standard with which obviousness is determined. *Hodosh v. Block Drug Co., Inc.*, 229 USPQ 182, 187 n.5 (Fed. Cir. 1986).

The Office has highlighted claims 1-3 of Brodbeck '311 which recites a Markush group of over 20 different types of biocompatible polymers and then asserts that Brodbeck "teach mixtures of lactic acid polymers in the molecular weight range of from 1,000 to 120,000." Office Action at page 5. Markush group language is a form of alternative expression that is unique to U.S. patent practice. The grouping recites members a being "selected from the group consisting of A, B and C." See *Ex parte Markush*, 1925 C.D. 126 (Comm'r Pat. 1925). In Brodbeck '311, the Markush group in claim 2 instructs one to select a biocompatible polymer selected from the 20 or so different types of polymers (polylactides, polyglycolides, polycaprolactones, etc. "and mixtures thereof." Brodbeck '311, claim 3. The Office believes that this language instructs the skilled person to select mixtures of lactide polymers having different molecular weights. Applicants respectfully disagree. Initially, claim 5 of Brodbeck '311

instructs that the singular "lactic acid-based polymer", not "polymers", has a MW between 1,000 and 20,000. Accordingly, the Office has based its rejection on a misreading of the actual Brodbeck '311 claim language. Claim 5 of Brodbeck '311 recites that when a lactide-based polymer is the selection from the Markush group, it will have a certain size within the recited range. In addition, the "mixture" language that the Office has identified from claim 2 has likewise been misinterpreted. The skilled person in the polymer arts knows that common biocompatible polymers include co-polymers, for example, polylactide-co-glycolide, or PLGA, and co-polymers of polylactide and caprolactone just to name a few of the more common co-polymer systems. The intent to include co-polymers, not just homopolymers in the Markush group is a more accurate reading of that language then. Accordingly, the Office has based its rejection on two mis-readings of the actual Brodbeck '311 claim language. The Office's assertion that the skilled person, when reading Brodbeck '311 as a whole for what it fairly teaches, would understand the Markush group language to expressly of implicitly instruct selection of mixtures of lactide polymers having different molecular weight is simply not supported by the record and applicants respectfully submit that it is improper. Looking at the Brodbeck '311 working examples (Examples 1 and 2, columns 9 and 10), it is plain to see that Brodbeck '311 selected a 50:50 lactic acid:glycolic acid copolymer, and the actual language of claim 2 was intended to cover the selection of such co-polymers from the Markush group.

The Office has further looked to the secondary reference to Ravivarapu and asserted that it teaches "the concept of combining PLGA polymers that varied in the molecular weights in various ratios [to yield] microspheres with varied drug release profiles". Office Action at page 7. The Office then concludes that the skilled person would know that the Brodbeck '311 gel systems could be modified in a manner similar to the Ravivarapu microspheres, and would have a "reasonable expectation of success in producing the claimed invention." Office Action at page 10. Applicants respectfully disagree.

Applicants submit that the relevant level of skill in the art is fairly high, with the ordinarily skilled person being a controlled-release pharmaceutical formulation chemist

with sufficient experience and training to understand the basic mechanisms involved with controlled-release polymer systems, and the fundamental differences between alternative controlled-release systems. Ravivarapu is clearly directed to microsphere technology. This is recognized by the Office at pages 7, 8, 9 10 and 11. Microspheres are solid structures, and in the case of Ravivarapu, they are formed using lactide polymers. After administration, the only way for the active agent to release from the solid microsphere is by way of a constant destruction of the solid matrix by degradation, particularly the microspheres are hydrated by the aqueous tissue environment, causing swelling and cracking of the solid polymer matrix, and exposing and thereby releasing active agent over time. The active agent cannot "swim" or otherwise move out of the matrix, so the basic mechanism of action for the Ravivarapu microsphere controlled release system is selection of polymers that degrade more quickly, thereby allowing earlier release of the active agent from the microspheres. In the selection of Ravivarapu that the Office has recited at page 8 of the Office Action, the idea of enhanced degradation is underlined by the Office (top of the page), and the faster hydration is underlined by the Office in the following sentence. Finally, the expectation that this provides quicker drug release is the final section that was underlined by the Office.

In contrast, Brodbeck '311 teaches a gel system that is injected and remains as a gel in the tissue after implantation. The basic mechanism of controlled release in such systems is diffusion of the active agent through the gel matrix. Biodegradable polymers are used to allow for subsequent clearance of the controlled release matrix, such that the matrix does not have to be surgically removed after the intended delivery period. Since controlled release from the Brodbeck '311 gel is dependent on the matrix remaining intact, thereby providing a constant (diffusional) control over the rate at which the active agent is released, the skilled person would not intentionally seek to rapidly degrade the polymer gel matrix. In other words, the skilled person would simply not look to rapidly degrading solid microsphere systems in order to improve or modify the Brodbeck '311 gel. In like manner, the skilled person would not look to gel-based technologies to improve or modify solid microsphere systems. The two systems are simply incompatible and operate by entirely different mechanisms of action. Modifying a gel to hydrate and

degrade more rapidly would disrupt the gel system and frustrate the basic mechanism of action (controlled diffusion of the active agent through the intact gel matrix). Modifying a solid microparticle to resist hydration and degradation would frustrate the basic mechanism of action of that system (rapid hydration and degradation of the solid matrix to expose and release the active agent).

This is strong evidence of nonobviousness as noted by the Supreme Court in *KSR* emphasizing that consideration of prior art that teaches away from the claimed invention is also relevant to the determination of obviousness. In particular, the Court stated that ***"when the prior art teaches away from combining certain known elements, discovery of a successful means of combining them is more likely to be nonobvious."*** *KSR Int'l Co. v. Teleflex Inc.*, 127 S. Ct. 1727 (2007). See also, *Dystar Textilfarben GmbH v. C.H. Patrick Co.*, where the Federal Circuit stated that "[once] all claim limitations are found in a number of prior art references, the factfinder must determine '[w]hat the prior art teaches, ***whether it teaches away from the claimed invention***, and whether it motivates a combination of teachings from different references.' *Dystar Textilfarben GmbH v. C.H. Patrick Co.*, 464 80 U.S.P.Q.2d 1641, 1646 (Fed. Cir. 2006), *citing In re Fulton*, 391 F.3d 1195, 1199-1200 (Fed. Cir. 2004) (*emphasis added*). Finally, as stated in the MPEP, "[i]f [the] proposed modification would render the prior art invention being modified unsatisfactory for its intended purpose, then there is no suggestion or motivation to make the proposed modification. M.P.E.P § 2143.01. The Federal Circuit has stated a similar principle in *In re Gordon*, indicating that where the proposed modification would render the prior art invention unsatisfactory for its intended purpose, the prior art invention effectively teaches away from the proposed modification. *In re Gordon*, 733 F.2d 900, 902 (Fed. Cir. 1984).

Accordingly, the Office's proposed combination fails to establish a *prima facie* showing of obviousness of applicants' recited compositions. A proper reading of Brodbeck '311 reveals that the Office's assertion of disclosure of mixtures of lactide polymers having different molecular weights is simply incorrect. The Office's reliance on the primary reference to Brodbeck '311 to teach applicants' recited mixtures of two or three different molecular weight lactide polymers is based on two basic misreadings of

the Brodbeck '311 disclosure. In addition, the skilled person would not take guidance or inspiration from Ravivarapu's teaching of how to speed up hydration and degradation of solid microspheres and apply it to the Brodbeck '311 gel systems as argued by the Office. This would be expected to render the Brodbeck '311 gel unsatisfactory for its intended purpose. In light of this expectation, there cannot have been a reasonable expectation of success for the Office's asserted combination. The other secondary references to Brodbeck '200 and Penco add nothing to this fatal flaw in the Office's required *prima facie* showing of obviousness.

Accordingly, the Office's assertion that the skilled person would intentionally combine the Brodbeck '311 and Ravivarapu teachings to somehow arrive at applicants' recited compositions defies the common sense understanding that the skilled person has regarding these alternative systems. No matter which way you look at the Office's proposed combination, using one reference to modify the other simply destroys the operability of the modified system. Here again, applicants wish to point out that where a proposed modification would render the prior art invention unsatisfactory for its intended purpose, the prior art invention effectively teaches away from the proposed modification (*In re Gordon*, 733 F.2d 900, 902 (Fed. Cir. 1984)), and where a proposed modification would render the prior art invention being modified unsatisfactory for its intended purpose, there is no suggestion or motivation to make the proposed modification. M.P.E.P § 2143.01.

For all of the foregoing reasons, then, the rejection of claims 2, 3, 6, 9-19, 28-35, 37-47 and 84 under 35 U.S.C. §103(a) is improper. Reconsideration and withdrawal of the rejection is thus earnestly solicited.

CONCLUSION

Applicants submit that the pending claims define an invention that is both novel and nonobvious over the cited art, and thus all claims are in condition for allowance. Acknowledgement of this by the Office in the form of an early allowance is thus

respectfully requested. In addition, if the Examiner contemplates other action, or if a telephone conference would expedite allowance of the claims, applicants invite the Examiner to contact the undersigned at (408) 777-4915.

The appropriate fee is either attached or authorized. If the Commissioner determines that an additional fee is necessary, the Commissioner is hereby authorized to charge any additional fees associated with this communication or credit any overpayment to Deposit Account No. **50-1953.**

Respectfully submitted,

Date: 17 April 2009

Thomas P. McCracken
Registration No. 38,548

For and on behalf of
DURECT CORPORATION
10240 Bubb Road
Cupertino, CA 95014
Phone: (408) 777-4915
Fax: (408) 777-3577